method of Jurd and Horowitz,[6] both the reference patuletin and compound A-1 behaved exactly alike. Each exhibited a 4-mμ shift of the short wave-length band, after 5 min., from 257 mμ to 261 mμ in the presence of sodium acetate. With boric acid-sodium acetate mixture,[6] there was a shift of 18 mμ for each in the higher wave-length peak, indicating the presence of the *o*-dihydroxy group in both. In sodium ethoxide, however, the higher wave-length peak disappeared in each case after 5 min. Thus, patuletin and compound A-1 are identical by every test used.

Identification of compound A-2. The yellow powder (75 mg.), containing compound A-2 obtained from the faster-moving eluate of the silicic acid column, was crystallized twice from benzene–methyl alcohol to yield fine yellow needles. These were dried at 110°, *in vacuo;* m.p. 235–236°. R_f values in 60% acetic acid; the *n*-butyl alcohol–acetic acid–water; and the phenol-water solvent systems were 0.56, 0.85, and 0.88, respectively. The ultraviolet absorption spectrum showed maxima at 257 and 373 mμ and minima at 241 and 287 mμ.

Anal., Calcd. for $C_{17}H_{14}O_8$ (346.28): C, 58.96; H, 4.08; OCH_3, 17.92. Found: C, 59.12; H, 4.03; OCH_3, 18.57.

Compound A-2 (10 mg.) was methylated with 1 ml. of dimethyl sulfate in 8 ml. of anhydrous acetone and 2.5 g. of potassium carbonate to give colorless needles, m.p. 143–144°, not depressed by authentic quercetagetin hexamethyl ether. Demethylation of compound A-2 with hydriodic acid, sp. gr. 1.7, and acetic anhydride yielded quercetagetin. The latter had R_f values of 0.27, 0.45, and 0.20, respectively, in the 60% acetic acid, *n*-butyl alcohol–acetic acid–water, and phenol-water systems.

Degradation with potassium hydroxide by a procedure used previously by Yang *et al.*[7] produced vanillic acid. Identification of vanillic acid was achieved by the method of Hergert and Goldschmid.[8] Thus, compound A-2 contained the 3′-methoxy-4′-hydroxy grouping. Compound A-2 on paper chromatograms gave a greenish-yellow color under long wavelength ultraviolet light, indicating that its 3-hydroxy group is not substituted. Spectral shift measurements[5,6] indicated that a free 7-hydroxy group is present, as the short wave length band shifts from 257 mμ to 269 mμ with sodium acetate. Boric acid–sodium acetate addition produced no shift for the higher wave length peak, indicating the absence of an *o*-dihydroxy group. In 0.002*N* sodium ethoxide, the longer wave-length peak was partially suppressed after 5 min., and disappeared after 1 hr. These data indicate that compound A-2 is the 3′,6-dimethyl ether of quercetagetin.

Both patuletin and quercetagetin-3′-6-dimethyl ether have also been isolated from fresh spinach leaves obtained from a wholesale produce company. Other flavonoid compounds have been shown by paper chromatography to be present in both the fresh spinach and frozen spinach preparations. Studies on their identification are now in progress.

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Reaction of Indoles with Acetyl Cyanide

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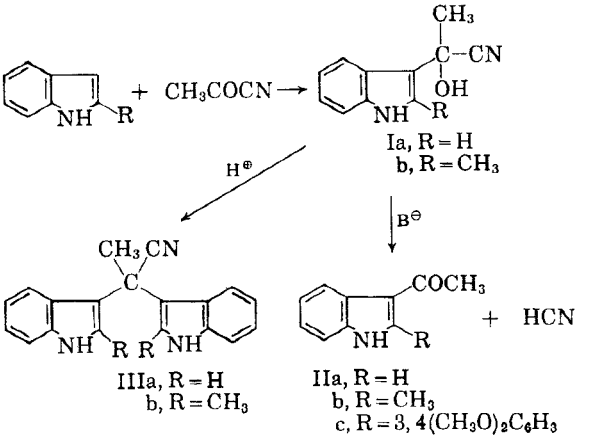
3-Acetylindole (IIa) is an important intermediate[2] in projected syntheses of several indole alkaloids and is available in moderate yield from indole and a boiling acetic acid–acetic anhydride mixture, the resultant 1,3-diacetylindole being readily converted into 3-acetylindole by base.[3] In an attempt to prepare this compound more economically, indole was treated with acetyl cyanide. Acyl cyanides are known to be effective acylating agents under a wide variety of conditions[4] and, in particular, acetyl cyanide in chloroform solution in the presence of pyridine has been reported to react with 2-methylindole forming 3-acetyl-2-methylindole (IIb) exclusively.[5]



The reaction of indole with acetyl cyanide in chloroform and in the presence of base, either at room temperature or at 62°, gave only a small amount of 3-acetylindole, the main product being a crystalline compound of empirical formula $C_{19}H_{15}N_3$. This same product was obtained almost exclusively on heating indole in an excess of acetyl cyanide. It gave a positive reaction with Ehrlich's reagent only on warming, and its infrared spectrum showed absorption bands at 3425 cm.$^{-1}$ (>NH), 2237 cm.$^{-1}$ (—CN), and those characteristic of the *o*-disubstituted benzene nucleus.[6] Its ultraviolet

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absorption spectrum was indolic in character (λ_{max}. 225, 280, 290 mμ; log ε 4.42, 4.14, and 4.08) and corresponded very closely to that of 1-cyano-1,1-di-(2-methyl-3-indolyl)ethane (IIIb), obtained from 2-methylindole and acetyl cyanide in chloroform in the presence of acid.[5] With the known preference for orientation to the 3-position of the indole nucleus, these results indicate that this $C_{19}H_{15}N_3$ product is 1-cyano-1,1-di(3-indolyl)ethane (IIIa). The NMR spectrum of (IIIa) in the 3–3.5 τ region was too complicated for the definite assignment of any band to the α-proton of the indole nucleus.[7]

Reexamination of the base-catalyzed reaction of acetyl cyanide with 2-methylindole has shown that besides the acetyl compound approximately 5% of the cyano compound (IIIb) is formed.

The intermediate cyanohydrin[8] (I) can react further in two ways. Electron donating groups in the 2-position would facilitate its base-catalyzed decomposition[4b,9] to the corresponding acetyl compound, as occurs with *p*-substituted benzaldehyde cyanohydrins containing electron-releasing groups in the *para* position.[10] The alternative mode of decomposition, analogous to the formation of diindolylmethanes,[11,12] involves a competing nucleophilic displacement of hydroxide ion by a second indole nucleus to give a compound such as (IIIa), and in the absence of electron-releasing substituents, or in the presence of acid, this mode of decomposition predominates.

This influence of the 2-substituent was further established by the formation of 3-acetyl-2-(3,4-dimethoxyphenyl)indole (IIc) from 2-(3-4-dimethoxyphenyl)indole and acetyl cyanide in the presence of base, whereas 2-phenylindole does not react under these conditions.[5]

EXPERIMENTAL

Condensation of indole and acetyl cyanide. A. Without solvent. Indole (1.2 g.; 0.01 mole) and acetyl cyanide[13] (2.0 g.; 0.03 mole) were heated together under reflux in an atmosphere of nitrogen for 45 min. A small amount of hydrogen cyanide was evolved. After concentration of the red colored reaction mixture under reduced pressure on the water bath, methanol was added to the residual gum which finally crystallized. The crystals (0.4 g., m.p. 191–192°) were collected and a further 0.7 g. of the same product was recovered from the mother liquor. 1-Cyano-1,1-di-(3-indolyl)ethane crystallized from aqueous methanol as colorless, rhombohedral plates, m.p. 194–194.5°. With concentrated sulfuric acid it gave a light yellow coloration and with chromic acid a successive color change of orange to red, through brown to black, was observed.

Anal. Calcd. for $C_{19}H_{15}N_3$: C, 80.0; H, 5.3; N, 14.7. Found: C, 79.9; H, 5.2; N, 14.4.

B. With solvent in the presence of base. Indole (1.2 g.; 0.01 mole) and acetyl cyanide (2.0 g.; 0.03 mole) in dry chloroform (10 ml.) and 2 drops of pure pyridine were kept overnight at room temperature or heated under reflux for 4 hr. The solvent was removed under reduced pressure on the water bath and after standing the dark red residue partly crystallized. This was dissolved in a benzene-chloroform (5:1) mixture and chromatographed on acid-washed alumina (35 g., activity 1) using benzene as eluant. 1-Cyano-1,1-di(3-indolyl)ethane (0.7 g., m.p. 192°) was eluted first, followed by a very small amount of 3-acetylindole (0.03 g.) which after further purification was identified by comparison of its infrared spectrum with that of an authentic specimen.[3]

3-Acetyl-2-methylindole. 2-Methylindole (13.1 g.; 0.1 mole) and acetyl cyanide (6.9 g.; 0.1 mole) in dry chloroform (100 ml.) with pure pyridine (1 ml.) were heated under reflux for 2.5 hr. *in a well ventilated hood.* After about 1 hr. of heating, crystalline material started to separate from the red reaction solution. After cooling the reaction mixture to 0°, the pink crystalline material was collected, washed with a little cold chloroform, and dried (6.8 g., m.p. 199–200°). A further 6.2 g. of crystalline material was obtained by concentration of the mother liquor. An analytical sample was crystallized from benzene whence 3-acetyl-2-methylindole separated as small, white plates solvated with 0.5 mole of benzene, m.p. 200° (lit.,[14] m.p. 196°).

Anal. Calcd. for $C_{11}H_{11}NO \cdot {}^1/_2C_6H_6$: C, 79.2; H, 6.6; N, 6.6. Found: C, 79.1; H, 6.95; N, 6.8.

Drying in a vacuum at 100° completely removes the solvent of crystallization.

The residue from the above mother liquor was continuously extracted in a hot Soxhlet with boiling benzene for 3 days. This completely removed all the 3-acetyl-2-methylindole together with a little 1-cyano-1,1-di(2-methyl-3-indolyl)ethane, the residue (1.3 g., m.p. 199–200°) in the extraction thimble. Crystallization of this residue from aqueous acetone gave colorless needles, m.p. 229–230° with previous shrinking and slight frothing.[5] The infrared spectrum of this product was identical with that of the compound obtained under acid catalysis.

Anal. Calcd. for $C_{21}H_{19}N_3$: C, 80.5; H, 6.1; N, 13.4. Found: C, 80.4; H, 6.1; N, 13.9.

3-Acetyl-2-(3,4-dimethoxyphenyl)indole. 2-(3,4-Dimethoxyphenyl)indole[15] (1.0 g.; 0.004 mole) and acetyl cyanide (0.85 ml.; 0.012 mole) in dry chloroform (12 ml.) with 2 drops of pure pyridine were heated under reflux for 2 hr. Hydrogen cyanide was readily evolved. The solvent was removed under reduced pressure on the water bath and the viscous green residue dissolved in 100 ml. of boiling benzene (charcoal) which was then concentrated to small volume. After standing overnight, the crude 3-acetyl-2-(3,4-dimethoxyphenyl)indole (0.8 g., m.p. 215° with shrinking from 195°) was collected. A small amount of starting material was recovered from the mother liquor. After several crystallizations from benzene, the acetyl compound separated as colorless prisms, m.p. 230–231°.

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Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 73.2; H, 5.8; N, 4.7. Found: C, 73.5; H, 5.9; N, 4.9.

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Synthetic Furocoumarins. III.[1] 8-Acetyl-4,5′-dimethylpsoralene

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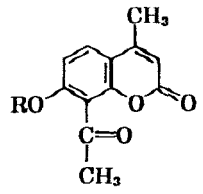
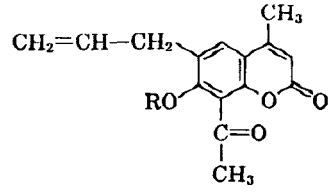
The method, described in earlier papers of this series[1] and developed for the synthesis of alkyl-substituted psoralenes, has been successfully applied to the synthesis of an acetylpsoralene. Samples of 8-acetyl-4,5′-dimethylpsoralene (VI) and its semicarbazone have thereby been made available for comparison of their photosensitizing activity with the very active 4,5′,8-trimethylpsoralene.[2] Details of the biological study are described elsewhere,[3] but it can be stated here that replacement of the 8-methyl group of 4,5′,8-trimethylpsoralene with an acetyl group or an acetylsemicarbazone group greatly reduces photosensitizing activity.

8-Acetyl-4-methyl-7-hydroxycoumarin[4] (I) was easily converted to 8-acetyl-7-allyloxy-4-methylcoumarin (II) by treatment with allyl bromide and anhydrous potassium carbonate in boiling acetone. Claisen rearrangement of II in boiling diethylaniline gave a 50% yield of 8-acetyl-6-allyl-7-hydroxy-4-methylcoumarin (III), which was characterized by the formation of an acetate (IV) with acetic anhydride and pyridine. Previous experiments[1] have shown that acetylation of 6-allyl-7-hydroxy coumarins is essential, to accomplish addition of bromine to the allyl double bond without simultaneous nuclear bromination. Acetylation was found to be unnecessary in this case, since 8-acetyl-6-allyl-7-hydroxy-4-methylcoumarin (III) smoothly added one molar equivalent of bromine to give a good yield of 8-acetyl-6-(2′,3′-dibromopropyl)-7-hydroxy-4-methylcoumarin (V). Presumably, the deactivating effect of the 8-acetyl group is sufficient to avoid nuclear bromination.

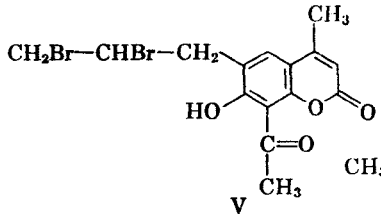
The final cyclization step presented difficulties not encountered in the synthesis of alkylpsoralenes[1,2] by this method. Treatment of V with sodium ethoxide in ethyl alcohol followed by acidification, gave a mixture of products, from which 8-acetyl-4,5′-dimethylpsoralene (VI), m.p. 165–165.5°, was



I. R = H
II. R = allyl



III. R = H
IV. R = acetyl



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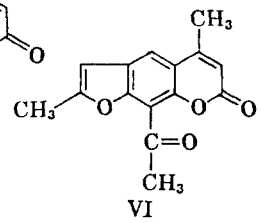

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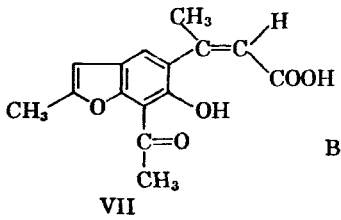
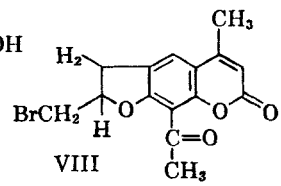


VII



VIII

isolated in 23% yield. In addition, 46% yield of a compound having the formula $C_{15}H_{14}O_5$, m.p. 159–160°, was obtained by alkaline extraction of the mixed products. The structure of *cis*-7-acetyl-6-hydroxy-2-methylbenzofuran-5-β-methylacrylic acid (VII) appears reasonable for this compound, since coumarinic acids with a chelating group (such as acetyl) *ortho* to the hydroxyl group have been shown to be stable.[5] Its infrared spectrum was consistent with structure VII, and treatment with three milliliters of glacial acetic acid, containing one drop of concentrated hydrochloric acid at room temperature, converted it to 8-acetyl-4,5′-dimethylpsoralene (VI).

In an effort to increase the yield of VI in the cyclization, 8-acetyl-6-(2′,3′-dibromopropyl)-7-hydroxy-4-methylcoumarin (V) was refluxed in *sym*-collidine for two hours. As before, a mixture of products was obtained but, in this case, 49% yield of a bromo compound $C_{15}H_{13}O_4Br$, m.p. 134.5–135.5°, was isolated. Its ultraviolet spectrum was quite similar to that of 8-acetyl-7-allyloxy-4-methylcoumarin (II) and did not shift in basic solution. It was insoluble in aqueous 5% sodium hydroxide and no OH absorption band could be found in its infrared spectrum. Although other structures are theoretically possible, 8-acetyl-5′-bromomethyl-4′,5′-dihydro-4-methylpsoralene (VIII) appears most likely for this substance. Additional evidence is required for a definite assignment.

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